U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

SEARCH REQUEST FORM

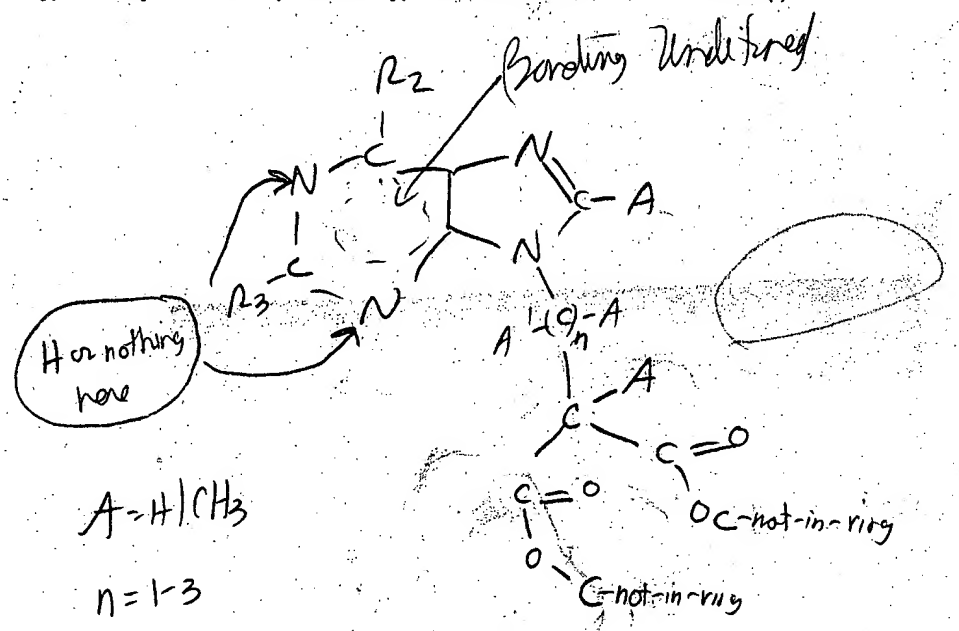
9-1141

Requestor's Name: BERCH Serial Number: 732479

Date: 9/30 Phone: 4718 Art Unit: 1202

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).



Cl 3-4 — R_2 = H / OH / OC / Hal / N(A)(A) = NH_2, NH-Me, N-Me-Me

R_3 = Hal / SC / N_3 (azido) / N(H/C)(H/C) = NH_2, NH-C, N(C)-C

MARK

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Total time:
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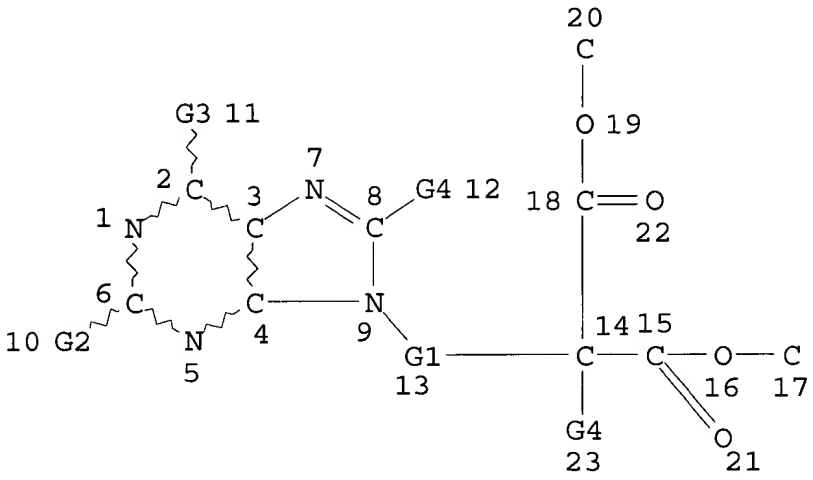

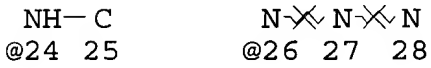

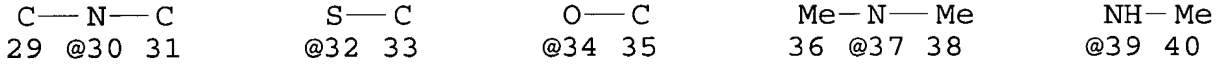

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VAR G3=H/OH/34/X/NH2/37/39
VAR G4=H/ME
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 40

STEREO ATTRIBUTES: NONE
L3 5 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 40 ITERATIONS 5 ANSWERS
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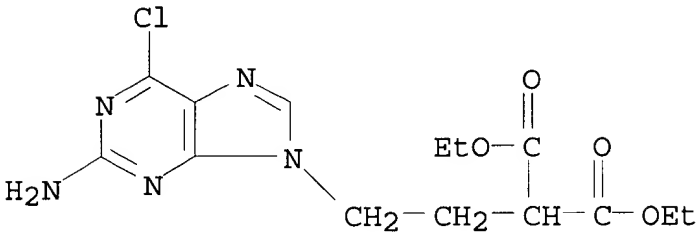
L3 ANSWER 1 OF 5 REGISTRY COPYRIGHT 1997 ACS
RN 177838-59-4 REGISTRY
CN Propanedioic acid, [2-(2-amino-6-chloro-9H-purin-9-yl)ethyl]-,

diethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C14 H18 Cl N5 O4
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 1: 125:34011 A direct approach to the synthesis of famciclovir and penciclovir. Choudary, Bernadette M.; Geen, Graham R.; Kincey, Peter M.; Parratt, Martin J.; Dales, J. Robert M.; Johnson, Graham P.; O'Donnell, Steven; Tudor, David W.; Woods, Neil (SmithKline Beecham Pharmaceuticals, Harlow, CM19 5AW, UK). Nucleosides Nucleotides, 15(5), 981-994 (English) 1996. CODEN: NUNUD5. ISSN: 0732-8311.

AB Reaction of 2-amino-6-chloropurine with tri-Et 3-bromopropane-1,1,1-tricarboxylate followed by decarbethoxylation/transesterification of the unpurified product was the key sequence in synthesizing both the anti-herpesvirus agent penciclovir and its oral form famciclovir in three isolated steps.

L3 ANSWER 2 OF 5 REGISTRY COPYRIGHT 1997 ACS
RN 172529-93-0 REGISTRY
CN Propanedioic acid, [2-(2-amino-6-chloro-9H-purin-9-yl)ethyl]-, dimethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
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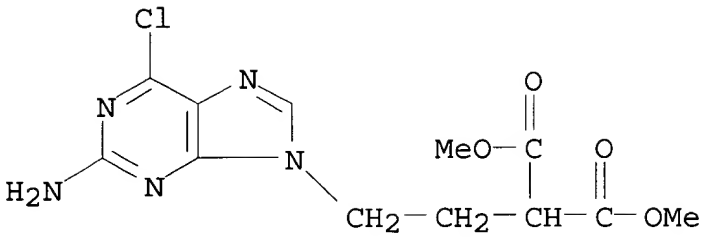
SR CA
LC STN Files: CA, CAPLUS, CASREACT



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REFERENCE 2: 124:86711 Preparation of antiviral purine derivatives. Dales, John Robert Mansfield (SmithKline Beecham PLC, UK). PCT Int. Appl. WO 9528402 A2 951026, 11 pp. DESIGNATED STATES: W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 95-EP1840 950419. PRIORITY: GB 94-7698 940419.

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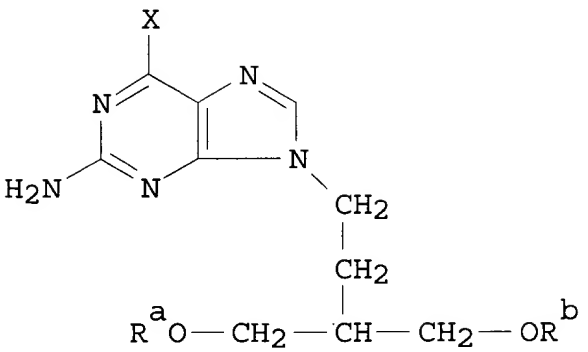

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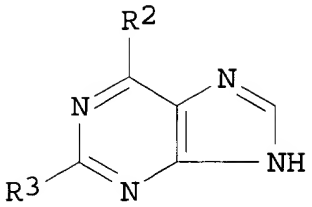

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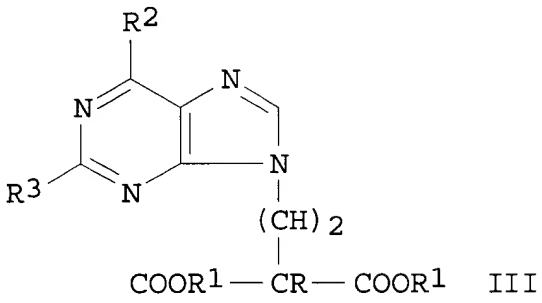


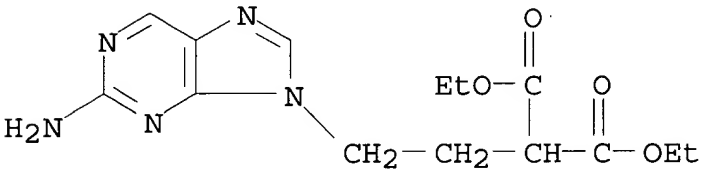
III

AB The title compds. [I; X is hydrogen, hydroxy, chloro, C1-6 alkoxy or Ph-C1-6 alkoxy; and Ra and Rb are hydrogen, or acyl or phosphate derivs. thereof] are prepd. via reaction of II [R2 is hydrogen, hydroxy, chlorine, C1-6 alkoxy, Ph C1-6 alkoxy or amino; R3 is halogen, C1-6 alkylthio, C1-6 alkylsulfonyl, azido, an amino group or a protected amino group] with L-(CH2)2-C(COOR1)3 wherein L is a leaving group and R1 is C1-6 alkyl, or Ph-C1-6 alkyl in which the Ph group is optionally substituted to give III [R = COOR1; R1-R3 same as above], decarboxylation of the latter to give III [R = H; R1-R3 same as above], followed by conversion of the latter to I. Thus, coupling of II [R2 = Cl, R3 = NH2] with Br-CH2-CH2-C(CO2Et)3 followed by decarboxylation gave III [R = H, R1 = Et, R2 = Cl, R3 = NH2], which was reduced with NaBH4 and then acetylated to give I [X = Cl, Ra = Rb = Ac], which was hydrogenolyzed over Pd/C to give the antiviral agent famciclovir [I; X = H, Ra = Rb = Ac]. Another antiviral agent, penciclovir, was prepd. similarly.

L3 ANSWER 3 OF 5 REGISTRY COPYRIGHT 1997 ACS
RN 122497-22-7 REGISTRY
CN Propanedioic acid, [2-(2-amino-9H-purin-9-yl)ethyl]-, diethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C14 H19 N5 O4

Searched By: Mary Hale 308-4258

SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMINFORMRX, USPATFULL
(*File contains numerically searchable property data)



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:34011 A direct approach to the synthesis of famciclovir and penciclovir. Choudary, Bernadette M.; Geen, Graham R.; Kincey, Peter M.; Parratt, Martin J.; Dales, J. Robert M.; Johnson, Graham P.; O'Donnell, Steven; Tudor, David W.; Woods, Neil (SmithKline Beecham Pharmaceuticals, Harlow, CM19 5AW, UK). Nucleosides Nucleotides, 15(5), 981-994 (English) 1996. CODEN: NUNUD5. ISSN: 0732-8311.

AB Reaction of 2-amino-6-chloropurine with tri-Et 3-bromopropane-1,1,1-tricarboxylate followed by decarbethoxylation/transesterification of the unpurified product was the key sequence in synthesizing both the anti-herpesvirus agent penciclovir and its oral form famciclovir in three isolated steps.

REFERENCE 2: 117:212870 Regiospecific Michael additions with 2-aminopurines. Geen, Graham R.; Kincey, Peter M.; Choudary, Bernadette M. (SmithKline Beecham Pharm., Pinnacles/Harlow/Essex, CM19 5AD, UK). Tetrahedron Lett., 33(32), 4609-12 (English) 1992. CODEN: TELEAY. ISSN: 0040-4039.

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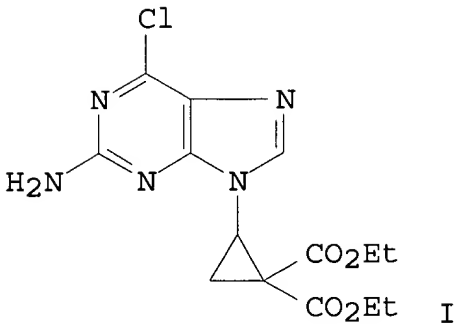

I

AB N-9-Alkylated materials are the sole products obtained from reaction of 2-aminopurines (potential guanine precursors) with Michael acceptors for an extended period of time. Thus, 2-amino-6-chloropurine was treated with ClCH2CH:C(CO2Et)2 to give the cyclopropane deriv. I which was converted to famciclovir by redn. in 2 steps.

REFERENCE 3: 115:28993 Preparation of purine acyclonucleoside intermediates. Geen, Graham Richard; Grinter, Trevor John; Moore, Stephen (Beecham Group PLC, UK). Eur. Pat. Appl. EP 420559 A2 910403, 15 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 90-310444 900925. PRIORITY: GB 89-22076 890928.

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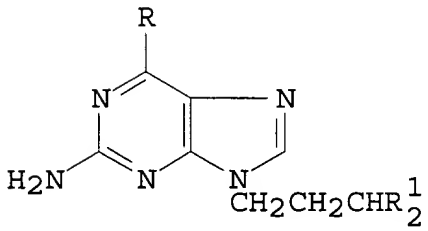

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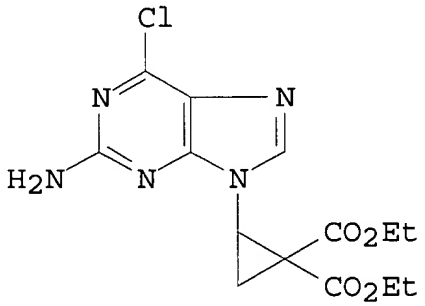

II

AB Acyclonucleoside I (R = H, OH, Cl, alkoxy, phenylalkoxy; R1 = CH2OH) intermediates I (R1 = CO2R2, R2 = alkyl, phenylalkyl) were prepd. from a purine deriv. and a haloalkylidenemalonate. Thus, 2-amino-6-chloropurine was treated with BrCH2CH:C(CO2Et)2 to give 78% cyclopropane II which was hydrogenated over Pd to give 38% I (R

= H, R1 = CO2Et).

REFERENCE 4: 112:7269 Preparation of 2-amino-9-[4-hydroxy-3-(hydroxymethyl)butyl]purines as pharmaceutical intermediates. Grinter, Trevor John; Geen, Graham Richard; Parratt, Martin John (Beecham Group PLC, UK). Eur. Pat. Appl. EP 302644 A2 890208, 27 pp. DESIGNATED STATES: R: BE, CH, DE, ES, FR, GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 88-306836 880725. PRIORITY: GB 87-18283 870801; GB 88-13926 880613.

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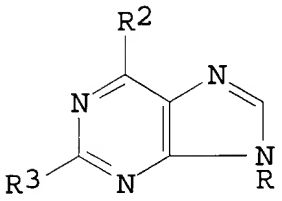

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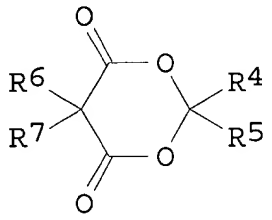

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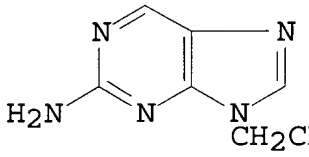


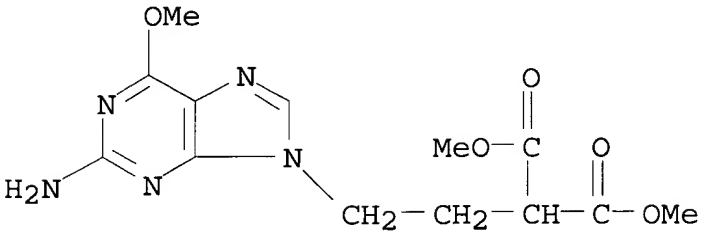
IV

AB The title compds. [I in which R = CH2CH2CH(CH2ORa)CH2ORb; Ra, Rb = H, acyl, phosphate residue; R2 = H, OH, Cl, alkoxy, phenylalkoxy; R3 = NH2] (II) were prepd., in 1 variant, by condensation of dioxaspirooctanedione III (R6R7 = CH2CH2; R4, R5 = H, alkyl, Ph; R4R5 = alkylene) with I in which R = H, followed by transesterification and redn. steps. I (R = H, R2 = Cl, R3 = NH2) was stirred overnight at 40.degree. with BrCH2CH2C(CO2Et)3 in DMF contg. K2CO3 and the N-7-alkylated product was refluxed 2 h with Pd/C in MeOH contg. HCO2NH4 to give I [R = CH2CH2C(CO2Et)3, R2 = H, R3 = NH2] which was stirred 1 h with Na in EtOH to give I [R = CH2CH2CH(CO2Et)2, R2 = H, R3 = NH2]. The latter was refluxed 1 h with NaBH4 in Me3COH with MeOH addn. to give title compd. IV.

L3 ANSWER 4 OF 5 REGISTRY COPYRIGHT 1997 ACS
RN 122497-21-6 REGISTRY
CN Propanedioic acid, [2-(2-amino-6-methoxy-9H-purin-9-yl)ethyl]-, dimethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C13 H17 N5 O5

Searched By: Mary Hale 308-4258

SR CA
LC STN Files: CA, CAPLUS, USPATFULL



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REFERENCE 2: 112:7269 Preparation of 2-amino-9-[4-hydroxy-3-(hydroxymethyl)butyl]purines as pharmaceutical intermediates. Grinter, Trevor John; Geen, Graham Richard; Parratt, Martin John (Beecham Group PLC, UK). Eur. Pat. Appl. EP 302644 A2 890208, 27 pp. DESIGNATED STATES: R: BE, CH, DE, ES, FR, GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 88-306836 880725. PRIORITY: GB 87-18283 870801; GB 88-13926 880613.

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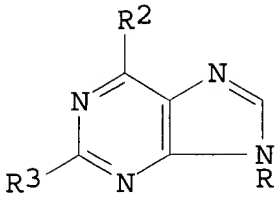

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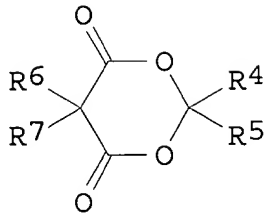

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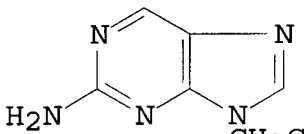

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RN 122497-20-5 REGISTRY
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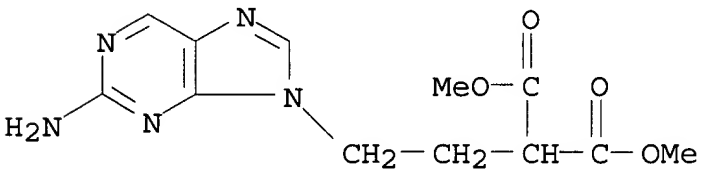
FS 3D CONCORD
MF C12 H15 N5 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



Searched By: Mary Hale 308-4258

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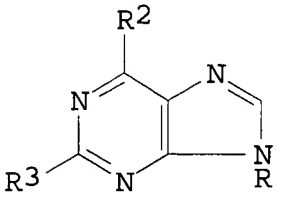
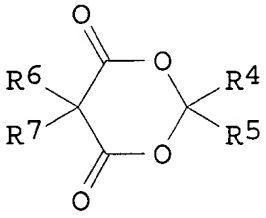


I



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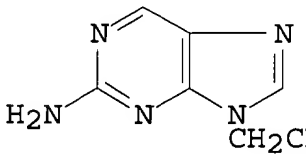

IV

AB The title compds. [I in which R = CH2CH2CH(CH2ORa)CH2ORb; Ra, Rb = H, acyl, phosphate residue; R2 = H, OH, Cl, alkoxy, phenylalkoxy; R3 = NH2] (II) were prepd., in 1 variant, by condensation of dioxaspirooctanedione III (R6R7 = CH2CH2; R4, R5 = H, alkyl, Ph; R4R5 = alkylene) with I in which R = H, followed by

transesterification and redn. steps. I (R = H, R2 = Cl, R3 = NH2) was stirred overnight at 40.degree. with BrCH2CH2C(CO2Et)3 in DMF contg. K2CO3 and the N-7-alkylated product was refluxed 2 h with Pd/C in MeOH contg. HCO2NH4 to give I [R = CH2CH2C(CO2Et)3, R2 = H, R3 = NH2] which was stirred 1 h with Na in EtOH to give I [R = CH2CH2CH(CO2Et)2, R2 = H, R3 = NH2]. The latter was refluxed 1 h with NaBH4 in Me3COH with MeOH addn. to give title compd. IV.

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